Mirtazapine Treatment for Comorbid Anxiety / Depressive Disorders in Young Subjects with Attention-Deficit Hyperactivity Disorder: Case Series

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ÖZET:

Dikkat eksikliği hiperaktivite bozukluğu olan çocuk ve ergenlerde komorbid anksiyete / depresif bozuklukların tedavisinde mirtazapin kullanımı: olgu serisi

Amaç: Dikkat eksikliği hiperaktivite bozukluğu (DEHB) olan ve metilfenidat tedavisi alan çocuk ve ergenlerde komorbid anksiyete / depresif bozuklukların tedavisinde mirtazapinin etkinliği ve tolerabilitesini araştırmak.
Yöntem: DSM-IV'e göre DEHB ve komorbid anksiyete ya da depresif bozukluk tanısı alan olgulara hem anksiyete/depresif bozukluklara yönelik hem de metilfenidatla ilişkili yan etkileri gidermek ya da Seçici Serotonin Gerialım Önleyicisi (SSGÖ) ile ilişkili yan etkilerden kaçınmak için mirtazapin 7.5-15 mg/gün tedavisi başlandı. Hedef semptomlardaki iyileşme ilişkili ölçekler ve klinik global izlem-iyileşme (KGİ-İ) ölçeği kullanılarak değerlendirildi.
Bulgular: Olgular dört erkek ve üç kız çocuğundan oluşmaktaydı (yaş ortalaması 11.85±2.91 yıl). Metilfenidat ve mirtazapin tedavi süreleri sırasıyla 14.28±9.41 ve 3.71±0.95 aydı. Mirtazapin ortalama dozu 16±2.64 mg/gündü. Bütün olgular KGİ-İ ölçeğinde uyku probleminde oldukça ya da çok düzelme gösterirken üç olgu iştah probleminde oldukça düzelme gösterdi. Altı olgu KGİ-İ ölçeğinde anksiyete semptom /bozukluklarında hafifle çok arasında değişen düzelme gösterirken bir olguda depresyon oldukça düzelme gösterdi. Mirtazapin genel olarak iyi tolere edildi. En sık bildirilen yan etkiler iştah artması (n=5), kilo alımı (n=4; 1000-4000 gram; 1357.14±1546.88 gram); gün içi sedasyon (n=4) ve irritabiliteydi (n=2).
Sonuç: DEHB ve komorbid anksiyete/depresif bozuklukları olan çocuk ve ergenler, özellikle metilfenidat ya da SSGÖ ile ilişkili uyku ve iştah problemlerinin varlığında, metilfenidat tedavisine mirtazapin eklenmesinden fayda görebilirler.

Anahtar sözcükler: Anksiyete, DEHB, depresyon, komorbidite, mirtazapin, tedavi

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ABSTRACT:

Mirtazapine treatment for comorbid anxiety / depressive disorders in young subjects with attention-deficit hyperactivity disorder: case series

Objective: To investigate the efficacy and tolerability of mirtazapine combination with methylphenidate in young subjects with diagnosis of attention deficit hyperactivity disorder (ADHD) and comorbid anxiety or depressive disorders.
Method: Subjects with DSM-IV diagnosis of ADHD and comorbid anxiety or depressive disorders were added mirtazapine 7.5 or 15 mg/day initially to treat anxiety or depressive disorders as well as to counteract or avoid methylphenidate or SSRIs related side effects. Improvement in target symptoms were assessed using relevant scales and the Clinical Global Impression-improvement (CGI-I) scale.
Results: Subjects were four boys and three girls (11.85±2.91 years). Duration of methylphenidate and mirtazapine treatment was 14.28±9.41 and 3.71±0.95 months respectively. Final dose of mirtazapine was 16±2.64 mg/day. All subjects showed moderate to very much improvement in sleep and three subjects showed much improvement in appetite problems on CGI-I scale. Six subjects showed mild to very much improvement in anxiety disorders /symptoms and one subject showed much improvement in depression on CGI-I scale. Mirtazapine was generally tolerated well. Most frequently reported side effects were increased appetite (n=5), weight gain (n=4; 1000-4000 gm; 1357.14±1546.88 gm); day time sedation (n=4) and irritability (n=2).
Conclusions: Young subjects with diagnosis of ADHD and comorbid anxiety or depressive disorders may benefit from mirtazapine addition particularly in the presence of methylphenidate or SSRIs related sleep and/or appetite problems.

Key words: Anxiety, ADHD, depression, comorbidity, mirtazapine, treatment

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INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is a relatively common neuropsychiatric disorder that has an onset in childhood and has been estimated to occur in 3 to 7% of school-aged children around the world (1). If left untreated this disorder causes multidimensional impairment in patient's life including difficulties in academic performance as well as in emotional and adaptive functioning, and social and family relationships. Methylphenidate (MPH) has been the first line psychopharmacological treatment in children and adolescents with ADHD and results in significant improvement in 70–80% of affected children (2). Nausea, decreased appetite, weight loss, and sleep disturbances are among the most frequently reported side effects

during MPH treatment (2). These side effects may cause treatment noncompliance and may result in important long term consequences on patients' height and weight (2,3).

Meanwhile comorbid psychiatric disorders may be present in the majority of individuals diagnosed with ADHD and the presence of comorbid psychiatric disorders may complicate the clinical picture and the selection of optimal ADHD pharmacotherapy (4). In patients with ADHD, the prevalence of comorbid depressive disorders has been reported to range from 6% to 47% and anxiety disorders range from 25% to 45% (4-7). However pharmacotherapy guidelines for comorbid anxiety/ depressive disorders in subjects with ADHD are not well established, and findings of sparse treatment studies are inconsistent.

The present report is a case series that aims to provide data on the efficacy and tolerability of mirtazapine in the treatment of comorbid anxiety or depressive disorders in young subjects with ADHD who have been treated with MPH.

METHOD

Participants

Subjects in this study were either followed in or referred to a private child psychiatry clinic. All subjects met criteria for diagnoses of ADHD, anxiety and/or depressive disorders based on DSM-IV. In addition to their significant difficulties related to ADHD, all subjects also suffered from comorbid anxiety or depressive disorders. Those subjects have been on MPH treatment for a period ranging 4 to 30 months. Despite all subjects in this study showed moderate to very much improvement in ADHD symptoms with MPH treatment, majority of them developed significant sleep and appetite problems related to MPH treatment. Sleep problems pre-existed in three subjects and two of them worsened with MPH treatment. Remaining four subjects developed significant sleep problems after MPH treatment. Three subjects developed significant decrease in appetite and lost 2-4 kg. during MPH treatment. Four of the seven subjects had been treated with selective-serotonin reuptake inhibitors (SSRIs) for comorbid anxiety or depressive disorders. However they developed either new side effects (such as behavioral activation, gastrointestinal symptoms, or headache) or worsening previously existing sleep and appetite problems after SSRIs were added. Subjects in this study were prescribed additional mirtazapine to their treatment regimens due to presence of comorbid anxiety or depressive disorders that required medication treatment, presence of significant preexisting or MPH related sleep and appetite problems, and/or intolerance to SSRIs treatment.

Assessment & Procedure

The diagnosis of ADHD, anxiety and depressive disorders was made according to DSM-IV criteria using relevant modules of Schedule for Affective Disorders and Schizophrenia for School Age Children-Present and Lifetime Version-Turkish Version (K-SADS-PL-T) (8). The K-SADS-PL is a semi-structured diagnostic interview designed to assess current and past episodes of psychopathology in children and adolescents. The severity of anxiety /depressive symptoms, efficacy of MPH and mirtazapine treatment and improvement in sleep and appetite problems were assessed using standard scales; The Conner's short form for ADHD, The Screen for Child Anxiety Related Disorders (SCARED), The Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS), The Children's Depression Inventory (CDI) and The Clinical-Global-Impression improvement (CGI-I) scale. A side effect checklist was used to assess new onset side effects after mirtazapine was commenced. The subjects and parents were asked for their informed consent before initiation of mirtazapine treatment. An open trial of mirtazapine with 7.5 or 15 mg/day initial dosage was conducted for at least three months. Subjects continued prior MPH treatment without any dosage reduction and MPH dosage was increased in two subjects after mirtazapine was added.

RESULTS

Subjects were four boys and three girls with an age range of 8-16 years (11.85±2.91). DSM-IV diagnosis among this sample included ADHD combined (n=4) and inattentive (n=3) type, generalized anxiety (n=6), social anxiety (n=6), panic (n=2), separation anxiety (n=2), obsessive-compulsive (n=2) and major depressive

disorders (n=1), special phobia (n=2) and agoraphobia (n=1).

Duration of MPH and mirtazapine treatment ranged 4-30 months (14.28±9.41) and 2-5 months (3.71±0.95) respectively. Final dose of mirtazapine was 15-22 mg/day (16±2.64). All subjects showed moderate to very much (two subjects very much, three subjects much and two subjects moderate) improvement in sleep problems. Three subjects showed much improvement in appetite problems and related weight loss. Six subjects showed mild to very much improvement in anxiety disorders /symptoms with a mean decrease of 13±4 (range 6-18) in the SCARED scores. One subject showed much improvement in depression with the CDI scores decreasing from 34 to 18. While one subject showed mild improvement in OCD symptoms with a total CY-BOCS score decreasing from 18 to 15, another subject showed no improvement in OCD symptoms. Clinical characteristics and response to treatment of the subjects are presented in Table 1.

Table 1: Clinical Characteristics and Treatment Response of the Subjects

CASE	Age (year) / Sex / DSM-IV Diagnosis	Dosage and Duration of Treatment	Target Symptoms	CGI-Improvement Scale
1	16 / F / ADHDi, SoAD, GAD	IR MPH 15 mg/day; 12 months Mirtazapine 15 mg/day; 5 months	Anxiety Sleep problems Decreased appetite/ lost 3 kgs	Moderate to much improvement Very much improvement Much improvement
2	10 / M / ADHDc, MDD	OROS MPH 36 mg/day; 24 months Mirtazapine 15-22 mg/day; 4 months	Depression Sleep problems	Much improvement Moderate improvement
3	13 / F / ADHDi, SoAD, GAD	IR MPH 15-20 mg/day; 6 months Mirtazapine 15 mg/day; 3 months	Anxiety Sleep problems Decreased appetite; lost 4 kgs	Moderate to much improvement Much improvement Much improvement
4	8/ F / ADHDc, ODD, SAD, SoAD, GAD, AF, SP	OROS MPH 18 mg/day; 4 months Mirtazapine 7.5-15 mg/day; 4 months	Anxiety Sleep problems	Mild improvement Moderate improvement
5	9 / M / ADHDc, SAD, SoAD, GAD	IR /OROS MPH 10-18 mg; 12 months Mirtazapine 15 mg/day; 4 months	Anxiety Sleep/appetite problems; lost 2 kgs	Moderate improvement Much improvement
6	13 / M / ADHDc, SoAD, GAD, PD, SP, OCD	OROS MPH 18-54 mg/day; 30 months Mirtazapine 15 mg/day; 2 months	Anxiety Sleep problems OCD symptoms	Moderate to very much improvement Very much improvement Mild improvement
7	14 / M / ADHDi, SoaD, GAD, PD, OCD	OROS MPH 18-36 mg/day; 12 months Mirtazapine 15 mg/day; 4 months	Anxiety Sleep problems OCD symptoms	Much improvement Much improvement No improvement

Abbreviations: ADHDc/i: Attention deficit hyperactivity disorder/combined/ inattentive type; CGI: Clinical Global Impression; F: Female; GAD: Generalized Anxiety Disorder; IR: Immediate release; M: Male; MDD: Major Depressive Disorder; MPH: Methylphenidate; OCD: Obsessive-Compulsive Disorder; PD: Panic Disorder; SAD: Seperation Anxiety Disorder; SoAD; Social Anxiety Disorder; SP: Special Phobia

Side effects possibly related to mirtazapine treatment included increased appetite (n=5), weight gain (n=4; 1000-4000 gm; 1357.14±1546.88 gm); day time sedation (n=4), irritability (n=2), headache (n=1), emotional lability (n=1), fever (n=1) and dry mouth (n=1). Increased appetite and weight gain were, in fact, desirable clinical outcomes in three subjects due MPH related decreased appetite and weight loss of 2-4 kg. No one of the subjects had discontinued medication or required dosage reduction due to side effects.

DISCUSSION

Short and long-term side effects are major factors in treatment non-compliance and medication discontinuation during MPH treatment in subjects with ADHD (2,3). Sleep and appetite problems are among the most frequent and disturbing side effects during MPH treatment (2,3). Meanwhile comorbid psychiatric disorders, such as anxiety/depressive disorders, may complicate clinical picture and have important impact on selecting and response to pharmacotherapy in subjects with ADHD (4). Despite high rates of comorbidity, studies regarding the psychopharmacological treatment of comorbid anxiety/ depressive disorders in young subjects with ADHD seem to be limited in the literature. Several studies have reported inconsistent findings on the efficacy of SSRIs (9, 10) or atomoxetine (11-13) for the treatment of comorbid anxiety/depressive disorders in young subjects with ADHD. In addition to inconsistent results, it is important to note that sleep and appetite problems are also among the most frequently reported side effects during SSRIs or atomoxetine treatment (9-14). Four of the seven subjects

in this study could not tolerate past or recent SSRIs trial and all subjects had preexisting or MPH-related sleep/appetite problems. However because all subjects showed significant improvement in ADHD symptoms with MPH treatment, we dissuaded from discontinuation of MPH treatment. Considering these factors together we preferred adding mirtazapine to their treatment without discontinuing or decreasing MPH treatment.

Mirtazapine is a second generation antidepressant which has significant blockade effects on serotonergic (such as 5HT3), alpha adrenergic (such as α2 auto and heteroreceptors) and histaminergic (such as H1) receptors (15). It has been shown to be effective in the treatment of social, generalized anxiety, or depressive disorders in adult or young populations (16-20). Our rationale behind adding mirtazapine in these subjects included several reasons: Firstly, as it has been reported previously, mirtazapine would be effective in the treatment of anxiety or depressive disorders in these subjects (16-20). Secondly, long term effects of MPH treatment on height and weight have been a major concern in young subjects with ADHD (3). During MPH treatment nausea, decreased appetite, and weight loss are among the most frequently reported and distressing side effects for patients and their families (2). Three of the seven subjects in this study developed significant decrease in appetite and lost 2-4 kilograms during MPH treatment. Meanwhile, up to 50% of parents of children with ADHD report difficulties with their children's sleep, including difficulties initiating and maintaining sleep (21). It has been suggested that children with ADHD and sleep problems have poorer cognitive and behavioral outcomes than children with ADHD alone (21,22). Therefore sleep problems should be effectively managed in children with ADHD. Recent studies indicate that the majority of ADHD-related sleep difficulties may result from a combination of comorbidity (such as anxiety, depressive or conduct disorders) and medical treatment (23,24). Regarding our study subjects, three of them had preexisting sleep problems and all subjects had developed or worsened sleep problems after MPH was initiated. Mirtazapine has a higher affinity to 5HT3 receptors that provides a good anti-nausea effect against chemotherapy or SSRI related nausea (15,25,26). Meanwhile alpha adrenergic and histaminergic receptors blockade by mirtazapine usually results in sedation (15). Given these pharmacological characteristics increased appetite, weight gain, and sedation have been among the most frequently reported side effects during mirtazapine treatment (15-19,27). We hypothesized that sedative and appetite stimulating properties of mirtazapine would counteract and help improving MPH related sleep and appetite problems and, at the same time, MPH would help improving the possible morning sedation related with mirtazapine treatment. Kratochvil et al. (2005) reported that mirtazapine could be a choice of treatment in the presence of treatment induced insomnia and comorbid anxiety or depressive disorders in subjects with ADHD (28). Finally mirtazapine would be generally tolerated well and less likely to cause behavioral activation than SSRIs. Clinicians may dissuade from using SSRIs medications in children with ADHD given their potential for behavioral activation which may be particularly problematic in children with ADHD. Furthermore SSRIs may also cause or worsen sleep and appetite problems in children. One of the subjects developed significant behavioral activation characterized with increased hyperactivity, excessive talking, irritability, and aggressive behaviors with fluoxetine that was started for his depression. Three subjects developed or worsened significant sleep/appetite or other gastrointestinal problems or headache after SSRIs were added to their treatment. Previous studies with mirtazapine on young population reported that it was tolerated generally well and did not cause behavioral activation like SSRIs and, contrary to SSRIs, may cause increased appetite and sedation (18,19,27).

Coskun and Zoroglu (2008) previously reported a ten-year-old boy with diagnosis of ADHD and separation and generalized anxiety disorders that developed tactile / visual hallucinations and sleep/ appetite problems with MPH / fluoxetine combination (29). The subject was discontinued from fluoxetine and mirtazapine was added to MPH treatment for his anxiety, sleep, and appetite problems. He tolerated mirtazapine / MPH combination quite well with significant improvement in anxiety, sleep, and appetite problems without any hallucinations.

The subjects tolerated MPH and mirtazapine combination generally well. Mirtazapine was associated with mild to very much improvement in comorbid anxiety or depressive disorders. All subjects also showed moderate to very much improvement in sleep problems and three subjects showed much improvement in appetite problems on CGI-I scale after mirtazapine was added.

While majority of the subjects with comorbid anxiety

disorders did not report any significant change in core ADHD symptoms after mirtazapine was added, the subject with major depression reported a moderate improvement in hyperactivity, irritability, and aggression. However improvement in these symptoms in this subject could be due to the improvement in depression and decrease in symptoms of behavioral activation after discontinuation of fluoxetine rather than a direct effect of mirtazapine. However, the effect of mirtazapine on core ADHD symptoms may still worth further investigation.

This study has several important limitations, such as small sample size and uncontrolled nature that make it difficult to generalize from its findings. However the results of this study may contribute to the management of young subjects with diagnosis of ADHD and comorbid anxiety/depressive disorders with or without MPH related side effects. Combination of mirtazapine with MPH was safe and associated with significant improvement in comorbid anxiety or depressive disorders and MPH related side effects (such as sleep and appetite problems) in these subjects. Further well-designed, placebo controlled studies with larger samples are warranted to further investigate the efficacy and safety of mirtazapine and MPH combination in young population with diagnosis of ADHD and co-morbid anxiety or depressive disorders.

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